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On the Unproved Synergism of the Inhalation Toxicity of Fire Gas

by Y. Tsuchiya

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RÉSUMÉ

L'auteur fait l'examen critique des rapports concernant l'action synergique des mélanges de gaz toxiques et il vérifie, à l'aide du concept d'indice de toxicité qu'il a lui-même élaboré, la valeur des affirmations faites à ce sujet.

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On the Unproved Synergism of the Inhalation Toxicity of Fire Gas

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ABSTRACT

Reports on synergistic actions of toxic combustion gas mixtures generated in fires are critically reviewed and claims on synergism are tested by the toxicity index concept developed by the author.

INTRODUCTION

CARBON MONOXIDE (CO) IS THE MOST COMMON TOXIC GAS IN FIRES, BUT there are numerous published reports of the combined actions of CO when accompanied by another toxic gas, such as CO₂, HCN, HCl, HF, or NO_x. Among the various combinations of toxic gases, the combination of CO and HCN has most often been studied because of the similarities in their narcotic actions. This paper reviews briefly some of the work that has been done on combinations of toxic gases as they relate to the synergistic effects of these combinations. Synergism, according to Webster's 9th New College Dictionary (1983), is the "interaction of discrete agencies or agents such that the total effect is greater than the sum of the individual effects."

CO-HCN COMBINATION

An early report on the possible synergism of CO and HCN was by Hofer [1], who exposed cats to the two gases singly and in combinations.

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He found that 0.25% CO alone and 45 ppm HCN alone caused paralysis, while the same effect was achieved with a mixture of 0.1% CO and 18 ppm HCN. Hofer's experimental data and the present author's toxicity index calculations [2] are shown in Table 1. The toxicity index of an atmosphere containing toxic gases is expressed assuming simple addition of individual effects as follows:

$$\text{Toxicity index} = \Sigma C_e/C_l$$

where C_e is the concentration of a toxic gas and C_l is the lethal concentration of the same gas. In Table 1 and other tables, if the index of a two-component mixture is significantly smaller than unity, it would indicate synergism; if it is nearly unity, additive effect, and smaller than unity, no additive, or antagonism.

Moss and others [3] exposed rats to various concentrations of CO and HCN. The determined lethal concentrations were 0.5% for CO and 50 ppm for HCN. They measured the combined effect of CO and HCN by exposing rats for 30 minutes to mixtures of the gases in which the concentration of CO was 0.2 or 0.25% and that of HCN was at a level between 5 and 30 ppm. Their results are shown in Table 2, together with the author's toxicity index calculations. They speculated that the absorption of HCN increased the respiration rates of the rats, which in turn increased their intake of CO, resulting, possibly, in enhancing the toxic effects of the combined gases. However, in the writer's opinion, their study was inconclusive because of the individual variation of the rats and the small number of experiments (only four rats were killed).

Higgins and others [4] determined the LC_{50} (lethal concentration for 50% of the test specimens) for rats and mice when exposed to HF, HCl, NO_2 , or HCN singly and combined with CO. Concentrations of CO to achieve 25% COHb (carboxyhemoglobin) were used in the study of com-

Table 1. Combined effect of CO and HCN to produce paralysis in cats (from Hofer [1]).

CO %	HCN ppm	Effective Time min	Toxicity Index of the Atmosphere
0.25	0	57	1
0.20	9	45, 35, 65	$0.20/0.25 + 9/45.2 = 1.0$
0.15	27	25, —, —	$0.15/0.25 + 27/45.2 = 1.2$
0.10	18	45, 55, 60, 80 60, 90, 80	$0.10/0.25 + 18/45.2 = 0.8$
0	45.2	27, 19	1

Table 2. Combined effect of CO and HCN to produce death in rats
(from Moss and others [3]).

CO %	HCN ppm	Lethality	Toxicity Index of the Atmosphere
0.5	0		1
0.25	10	0/1	$0.25/0.5 + 10/50 = 0.7$
0.2	5	0/1	$0.2/0.5 + 5/50 = 0.5$
0.2	10	1/5	$0.2/0.5 + 10/50 = 0.6$
0.2	15	2/3	$0.2/0.5 + 15/50 = 0.7$
0.2	20	1/1	$0.2/0.5 + 20/50 = 0.8$
0.1	30	0/1	$0.1/0.5 + 30/50 = 0.8$
	50		1

bined effects; the concentrations were 1,500 ppm for mice and 2,100 ppm for rats. A group of 10 rats and 15 mice were exposed for 5 minutes and the mortality was determined 7 days later. Higgins and others [4] found that the combined gases did not enhance the toxicity effect over that of the individual gases.

Mohler [5], referring to the paper of Higgins and others [4], stated "toxic substances when inhaled together can exert a greater lethality than when inhaled alone." This statement gives quite the opposite meaning to what was given in the paper of Higgins and others. Mohler believed that the combination of CO and HCN enhanced their toxicity effects above that expected from mere addition. He analysed air transport accidents in which blood COHb and blood cyanide of victims were determined. It is difficult, however, to conclude synergism of the two gases from Mohler's data.

Lynch [6] exposed rats to CO and HCN singly and in combinations and measured the inhalation LC_{50} (concentration-time product that killed 50% of the test specimens). Using techniques of probit analysis, he concluded that within the sensitivity of the measurements the toxicities of the two gases appeared to be purely additive.

Pryor and others [7] determined the combined lethal effects on mice of four primary variables (temperature, oxygen depletion, CO, and CO₂) and one of three noxious gases (NO₂, SO₂, HCN). Some of their experimental data on CO and HCN are shown in Table 3. Though they claimed "dramatic synergistic effect with each of three noxious gases," the validity of their claim is questionable, because a close scrutiny of their data indicates that their experiments were not well designed. Furthermore, Pryor and others [7,8] used the following terms to describe the combined effect of the gases: "strong additive or

Table 3. Combined effect of CO, HCN and other variables on mice (from Pryor and others [7]).

CO %	HCN ppm	O ₂ %	CO ₂ %	Temp. °F	Time h	Survivors
0.075	0	16	30	85	4	7/10
0.075	5	16	30	100	4	10/10
0.075	10	16	30	100	4	8/10
0.075	30	16	30	100	4	0/10
0	100	21	0	85	4	9/10
0	150	21	0	85	4	0/10

synergistic," "strong combined-", "significant combined-", or "pronounced combined effect," from which it is not clear whether they meant synergistic effects or additive effects. These terms are not synonymous, for the term synergism has quite a distinct meaning.

Kimmerle [9] exposed 20 male rats to CO and HCN singly as well as to combinations of the two gases for 30 minutes and determined LC₅₀ values. His excerpted results and the present author's toxicity index calculations are shown in Table 4. Kimmerle stated that "the results indicate a synergistic toxic action and . . . agree with those which Moss and co-workers found." The statement, however, is hardly warranted by the analysis of his data as shown in Table 4.

Birky [10] applied the toxicity index calculation developed by the present author [2] to Kimmerle's results and concluded "no synergism has been proven to exist, contrary to Kimmerle's statement." He also examined the data of Pryor and others [7,8] and suggested that there was a "necessity for more careful experimental planning and analysis of resulting data."

Yamamoto [11] considered the ratio (r) of concentration-time products used in his experimental conditions (ct) and the lethal value (CT); the

Table 4. Combined effect of CO and HCN on rats, 30 minutes exposure, LC₅₀ (from Kimmerle [9]).

CO %	HCN ppm	Toxicity Index of the Atmosphere
0.55	0	1
0.44	38	$0.44/0.55 + 38/200 = 0.99$
0.33	45	$0.33/0.55 + 45/200 = 0.825$
0	200	1

latter was almost constant for a toxic gas in a range of concentrations. For lethality, $r = ct/CT = 1$. When the lethality was caused by a mixture of two toxic gases, he assumed the relation: $r_1 + r_2 + s \times r_1 \times r_2 = 1$. When the two gases have an additive effect, $s = 0$, synergism $s > 0$, and antagonism, $s < 0$. Instead of concentrations of gases, Yamamoto determined concentrations of blood cyanide and COHb and assumed that concentrations in the blood are proportional to those in gases. He generated HCN and CO by pyrolysing polyacrylonitrile and cotton respectively. He did not find synergism.

Purser and Grimshaw [12] exposed monkeys to oxidative pyrolysis products of polyurethane and polyacrylonitrile and determined incapacitation times. They compared the mean data for polyurethane and the regression line for polyacrylonitrile. Incapacitation occurred after 20 minutes in a mixture of 115 ppm HCN and 1016 ppm CO generated from polyurethane foams, and in the other case, after 22 minutes in 115 ppm HCN and 0 ppm CO generated from polyacrylonitrile. The effect of the presence of CO was small. Purser and Grishaw stated, "On theoretical grounds, a strong additive effect of CO and HCN would not be expected since the main effect of CO is to impair the carriage of oxygen in the blood and its delivery to the tissues, while that of HCN is to prevent the tissues from using the oxygen supplied."

Table 5. Combined effect of toxic components of fire gas.

Author	Year	Ref.	Components	Was Synergistic or Enhanced Effect Reported?	Comments
Hofer	1926	2	CO, HCN	Yes	
Moss	1951	3	CO, HCN	Yes	
Higgins	1971	4	CO, HCN and others	No	statistical
Pryor	1974	7	CO, HCN and others	Yes	
Kimmerle	1974	9	CO, HCN	Yes	
Mohler	1975	5	CO, HCN	Yes	
Lynch	1975	6	CO, HCN	No	statistical
Yamamoto	1976	11	CO, HCN	No	statistical
Harland	1982	21	CO, HCN	No	
Purser	1984	12	CO, HCN	No	
Sakurai	1984	13	CO, HCN and others	No	statistical
Gaume	1971	16	CO, CO ₂ , NH ₃	No	antagonistic
Saito	1976	17	CO, HCl	No	antagonistic
Wohlschlager	1976	18	HCl, HF, dust	No	statistical
Levin	1984	19	CO, CO ₂	Yes	no reported data
Crane	1985	20	CO, CO ₂	No	

Sakurai [13] exposed mice to six toxic gases, including CO, NH₃, NO₂, HCl, HCN, and CO₂, which he used singly and in two- or three-component mixtures, and measured the times for incapacitation and death. His data were examined by Tsuchiya and Nakaya using their numerical method [14] in which two- and three-component interacting effects were quantitatively evaluated. No synergism was found in combinations of CO-HCN and CO-HCN-CO₂ in the range of concentrations used in Sakurai's experiments.

OTHER TOXIC GAS COMBINATIONS

Von Oettingen [15] surveyed the possible synergistic action of CO with other gases and factors, including CO₂, benzene, H₂S, HCN, NO_x, temperature, and humidity. According to Von Oettingen certain factors may increase the toxicity of CO. High temperatures increase respiratory rates and hence, the absorption of CO. High humidities produce the same results. Increased concentration of CO₂ in the air, in the absence of appreciable reduction of O₂, causes deepening of respiration and distinct increases of COHb levels. Several investigators cited by Von Oettingen reported (between 1902 and 1928) that illuminating gas was more toxic than would be expected from its CO content. This is explained by the presence of various other contaminants, and does not necessarily imply the existence of synergistic effects.

Gaume and others [16] determined the collapse time of mice by exposing them to single, double, and triple gas mixtures of CO, CO₂, and NH₃. They found that double gas mixtures extended the time to collapse, and triple gas mixtures extended it further, indicating negative synergism or antagonism.

Saito [17] exposed mice to CO, CO₂, and HCl singly and in combinations, and found that with CO-HCl mixtures, deaths of mice were delayed longer than with CO only. In the presence of irritants such as NH₃ or HCl, respiration rates of test animals are reduced, resulting in a reduced intake of CO and a longer survival time.

Wohlschlager and others [18] exposed rats and mice for 60 minutes to HCl and HF singly and in combinations, and also, together with alumina dust. They used the probit analysis technique for examining their LC₅₀ values and found that the effect of two gases was additive; no potentiating or antagonizing effects were found. The addition of alumina dust had no effects on the animals.

Levin [19] reported a synergistic effect of CO and CO₂ and claimed that the synergistic effect was as much as a factor of two. She explained that the presence of relatively high concentrations of CO₂ stimulates

respiration and increases the intake of CO, resulting in a shorter survival time. A quantitative evaluation of Levin's experimental data, however, will be needed when they become available.

Crane [20] exposed rats to CO concentrations ranging from 5,500 to 14,000 ppm with or without added CO₂, concentrations of which were 8 and 10.4%. There was no change in the times-to-incapacitation or the times-to-death resulting from the addition of CO₂. Aware of Levin's work, Crane repeated his own experiments with mixtures of 5,000 ppm CO and from 4 to 13% CO₂, and again there was no significant change in effective times.

CONCLUSIONS

Claims in the literature of synergistic toxicity effects are not supported for one or more of the following reasons:

1. The term synergism has frequently been used incorrectly;
2. Incorrect conclusions have been reached from the experimental data;
3. Some experimental data suggested a combined effect that was larger than a simple additive effect, but valid statistical methods to detect synergism were not applied to the data available;
4. When a valid statistical method was applied to the available experimental data, no synergism was detected.

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